

U.S. Patent Application Serial No. 10/522,706
Amendment After Final dated 21 November 2007
Reply to Office Action dated 21 August 2007

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims

Claim 1 (Currently Amended): A method of preventing or treating diseases associated with endothelial dysfunction which comprises administering a therapeutically effective amount of at least one proteosome inhibitor to an individual in need thereof, wherein the amount is effective to enhance the expression of endothelial nitric oxide synthase (eNOS) and wherein the amount is in a nanomolar range.

Claim 2 (Previously Presented): The method according to claim 1, wherein the diseases associated with endothelial dysfunction are non-insulin related diseases.

Claim 3 (Currently Amended): The method according to claim 1, wherein the endothelial dysfunction is associated with atherosclerosis, in particular coronary sclerosis and coronary artery disease.

Claim 4 (Previously Presented): The method according to claim 1, wherein the endothelial dysfunction is associated with heart failure.

Claim 5 (Currently Amended): The method according to claim 1, wherein the endothelial dysfunction is associated with ischemic diseases selected from the group consisting of comprising ischemic diseases such as peripheral arterial occlusive disease, e.g. critical leg ischemia, myocardial infarction and ischemic diseases of organs, e.g. of the selected from the group consisting of kidney, spleen, brain, and lung.

U.S. Patent Application Serial No. 10/522,706
Amendment After Final dated 21 November 2007
Reply to Office Action dated 21 August 2007

Claim 6 (Currently Amended): The method according to claim 1, wherein the proteasome inhibitor is selected from a group ~~comprising:~~ consisting of aclacinomycin A, lactacystin, clastolactacystein, N-carbobenzoxy-L-leucinyl-L-leucinyl-L-leucinal (also referred to as MG132 or zLLL), the boric acid derivative of MG232, N-carbobenzoxy-Leu-Nva-H (also referred to as MG115), N-acetyl-L-leucinyl-L-leucinyl-L-norleucinal (also referred to as LLnL), N-carbobenzoxy-Ile-Glu(OBut)-Ala-Leu-H (also referred to as PS1; SEQ ID NO:1), carbobenzoxy-L-leucinyl-L-leucinyl-L-leucin-vinyl-sulfon, 4-hydroxy-5-iodo-3-nitrophenylacetyl-L-leucinyl-L-leucinyl-L-leucin-vinyl-sulfon (NLVS), pyrazyl-CONH(CHPhe)CONH(CHisobutyl)B(OH)₂, and benzyloxy-carbonyl(Cbz)-Leu-leuboro-Leu-pinacol-ester.

- a) ~~naturally occurring proteasome inhibitors comprising:
peptide derivatives which have a C terminal epoxy keton structure, C-lacton derivatives, aclacinomycin A, lactacystin, clastolactacystein;~~
- b) ~~synthetic proteasome inhibitors comprising:
modified peptide aldehydes such as N-carbobenzoxy L-leucinyl L-leucinyl L-leucinal (also referred to as MG132 or zLLL), or the boric acid derivative of MG232, N-carbobenzoxy Leu Nva H (also referred to as MG115), N-acetyl L-leucinyl L-leucinyl L-norleucinal (also referred to as LLnL), N-carbobenzoxy Ile Glu(OBut)-Ala-Leu H (also referred to as PS1) [SEQ ID NO:1];~~
- c) ~~peptides comprising:
an α,β-epoxyketone structure, vinyl sulfones such as, carbobenzoxy L-leucinyl L-leucinyl L-leucin-vinyl-sulfon or, 4-hydroxy-5-iodo-3-nitrophenylacetyl-L-leucinyl-L-leucinyl-L-leucin-vinyl-sulfon (NLVS);~~
- d) ~~Glyoxal or boric acid residues such as: pyrazyl-CONH(CHPhe)CONH(CHisobutyl)B(OH)₂ and dipeptidyl boric acid derivatives;~~
- e) ~~Pinacol esters such as: benzyloxycarbonyl(Cbz)-Leu-leuboro-Leu-pinacol-ester.~~

Claim 7 (currently amended): The method according to claim 1, wherein the proteasome inhibitor is selected from a group ~~consisting of~~ comprising PS-314 as a peptidyl boric acid

U.S. Patent Application Serial No. 10/522,706
Amendment After Final dated 21 November 2007
Reply to Office Action dated 21 August 2007

~~derivative which is N-pyrazinecarbonyl-L-phenylalanin-L-leucin-boric acid (C₁₉H₂₅BN₄O₄) (PS-314); PS-519 as a β-lacton and a lactacystin derivative which is 1R-[1S, 4R, 5S]-1-(1-Hydroxy-2methylpropyl)-4-propyl-6-oxa-2azabicyclo[3.2.0]heptane-3,7-dione (C₁₂H₁₉NO₄) (PS-519); PS-273 (morpholin-CONH-(CH-naphthyl)-CONH-(CH-isobutyl)-B(OH)₂) and its enantiomer; PS-293; PS-296 (8-quinolyl-sulfonyl-CONH-(CH-naphthyl)-CONH(-CH-isobutyl)-B(OH)₂); PS-303 (NH₂(CH-naphthyl)-CONH-(CH-isobutyl)-B(OH)₂); PS-321 as (morpholin-CONH-(CH-naphthyl)-CONH-(CH-phenylalanin)-B(OH)₂); PS-334 (CH₃-NH-(CH-naphthyl)-CONH-(CH-Isobutyl)-B(OH)₂); PS-325 (2-quinol-CONH-(CH-homo-phenylalanin)-CONH-(CH-isobutyl)-B(OH)₂; PS-352 (phenyalanin-CH₂-CH₂-CONH-(CH-isobutyl)l-B(OH)₂; PS-383 (pyridyl-CONH-(CHpF-phenylalanin)-CONH-(CH-isobutyl)-B(OH)₂); PS-341; and PS-1 (Z-Ile-Glu(OtBu)-Ala-Leu-CHO [SEQ ID NO:1]); PS-2 [Benzylloxycarbonyl]-Leu-Leu-phenylalaninal or Z-LLF-CHO or Z-Leu-Leu-Phe-CHO) PS-1; PS-519 as a β-lacton and a lactacystin derivative which is 1R-[1S, 4R, 5S]-1-(1-Hydroxy-2methylpropyl)-4-propyl-6-oxa-2azabicyclo[3.2.0]heptane-3,7-dione (C₁₂H₁₉NO₄); epoxomicin (C₂₈H₈₆N₄O₇) and eponemycin (C₂₀H₃₆N₂O₅).~~

Claim 8 (Currently Amended): The method according to claim 1, wherein the proteasome inhibitor is selected from a group consisting of comprising a peptide aldehyde, a peptide boronate, a peptide vinylsulfone, a peptide epoxyketone, a lactacystin, a peptide α-ketonaldehyde, an α-ketoamide, an indanonepeptide, a polyalkylenaldehyde, a polyphenol such as and cathechin-3-gallate.

Claim 9 (Currently Amended): The method according to claim 1, wherein the proteasome inhibitor is selected from a group consisting of comprising Z-Leu-Leu-Leu-al (MG132), Z-Ile-Glu(OtBu)-Ala-Leu-al (PS-1) [SEQ ID NO:1], CEP1612, pyrazylcarbonyl-Phe-Leu-boronate (PS-341), dansyl-Phe-Leu-boronate (DFLB), morpholinonaphthylalanin-Leu-boronate (MG273), NIP-Leu₃-vinylsulfone (NLVS), Tyr-Leu₃-VS [SEQ ID NO:2], NIP-Leu-Leu-Asn-VS, Ada-Tyr-Ahx₃-Leu₃-VS [SEQ ID NO:3], Ada-Lys(bio)-Ahx₃-Leu₃-VS [SEQ ID NO:4], Ac(Me)-Ile-Ile-Thr-Leu-EX (epoxomicin) [SEQ ID NO:5], dihydroeponemycin, lactacystin, clasto-lactacystin-beta-lacton (omuralid), PS-519, Ac-Leu-Leu-Nle-al (ALLN), 3,4-dichloroisocoumarin (DCI), 4-(2-aminoethyl)-

U.S. Patent Application Serial No. 10/522,706
Amendment After Final dated 21 November 2007
Reply to Office Action dated 21 August 2007

bezolsulfonylfluorid (pefablock SC), TMC-95-A, gliotoxin, (-)epigallocatechin-3-gallate (EGCG), ritonavir, lovastatin, aclacinomicin A (aclarubicin), and cyclosporin, wherein Z represents benzyl oxycarbonyl, ~~all~~ al represents aldehyde, VS represents vinylsulfone, NIP represents 3-nitro-4-hydroxy-5-iodophenylacetate, and bio represents biotin.

Claims 10-26 (Canceled).

Claim 27 (Previously Presented): The method according to claim 1, wherein the nanomolar range is between 1 and 100 nanomolar.

Claim 28 (Previously Presented): The method according to claim 1, wherein a single administration of the proteosome inhibitor produces a long-term enhancement of the expression of eNOS.

Claim 29 (Previously Presented): The method according to claim 1, wherein the long-term enhancement is for up to ten days.

Claim 30 (New): The method according to claim 1, wherein the proteosome inhibitor is MG132.